



Clinical Protocol Number BDX-00146

**An Observational Study Assessing the Clinical Effectiveness of
the VeriStrat® Test and Validating Immunotherapy Tests in
Subjects with Non-Small Cell Lung Cancer**

(INSIGHT)

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Biodesix, Inc.
2970 Wilderness Place, Suite 100
Boulder, CO 80301

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INVESTIGATOR STATEMENT OF PROTOCOL APPROVAL

Clinical Protocol Number BDX-00146: An Observational Study Assessing the Clinical Effectiveness of the VeriStrat® Test and Validating Immunotherapy Tests in Subjects with Non-Small Cell Lung Cancer.

The information contained in this protocol and all other information relevant to this study are confidential and proprietary information of Biodesix, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Biodesix.

I have read and I understand protocol BDX-00146, dated September 11, 2017 and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make all reasonable efforts to complete the study within the designated time and in accordance with all national, state, and local laws or regulations, including Federal Code of Regulations for GCP and ICH guidelines. I have read and understand all sections of the protocol, including Section 8, Administrative Considerations.

I will provide copies of the protocol and access to all information furnished by Biodesix Inc. to study personnel under my supervision. I will discuss the material with them to ensure that they are fully informed about the study and study procedures.

I understand that the study may be terminated or enrollment suspended at any time by Biodesix Inc., with or without cause, or by me if it becomes necessary to do so in the best interests of the study subjects.

Investigator Signature

Date

Investigator Printed Name

PROTOCOL SYNOPSIS

Title	An Observational Study Assessing the Clinical Effectiveness of the VeriStrat® Test and Validating Immunotherapy Tests in Subjects with Non-Small Cell Lung Cancer (INSIGHT)
Sponsor Study No.	BDX-00146
Phase	Observational Study
Sponsor	Biodesix
Study Center(s)	25-35 sites in the United States
Objective(s)	<p>Primary Objective</p> <ul style="list-style-type: none">• To describe physician treatment patterns pre- and post-VeriStrat testing at time of treatment decision or assessment. <p>Secondary Objectives which may be tested:</p> <ul style="list-style-type: none">• To determine whether immunotherapy test(s) stratify immunotherapy-treated subjects by overall survival.• To determine whether immunotherapy test(s) stratify immunotherapy-treated subjects by progression-free survival.• To compare outcomes between those classified as VeriStrat-Poor and VeriStrat-Good.• To compare outcomes in subjects classified as VeriStrat-Poor and VeriStrat-Good and treated with platinum-based therapy.• To compare outcomes in subjects classified as VeriStrat-Poor and VeriStrat-Good and treated with immunotherapy.• To compare outcomes in subjects classified as VeriStrat-Poor and VeriStrat-Good and treated with single agent chemotherapy.• To evaluate the longitudinal changes in VeriStrat classification over the course of the study.

Exploratory Objectives which may be tested:

- To determine whether immunotherapy test(s) stratify subjects treated with chemotherapy or targeted therapies by outcome.
- To observe the correlation between VeriStrat classification and immunotherapy test(s) classification at baseline and longitudinally.
- To describe the longitudinal changes in immunotherapy test classification over the course of the study.
- To determine whether immunotherapy test(s) stratify immunotherapy-treated subjects by other clinically meaningful factors or endpoints.
- To observe changes in GeneStrat™ status across lines of therapy.

Study Design

The primary purpose of this observational study is to assess the physician's clinical practice patterns while using the VeriStrat test in subjects with non-small cell lung cancer (NSCLC) whose tumors are epidermal growth factor receptor (EGFR) wild-type (negative) or have a tested unknown EGFR mutational status. This study will also attempt to further validate that the VeriStrat test stratifies subjects by clinical outcomes in the uncontrolled clinical setting while exploring if certain therapeutic approaches may yield opportunities for further study.

Predictive and prognostic tests that aid in therapeutic decision making are critical for optimizing patient outcomes while minimizing toxicity and associated treatment costs. This study will also provide data to support Biodesix new classifier development.

Subjects who have been diagnosed with NSCLC, at any line of treatment who are EGFR wild-type (negative) or a tested unknown and who are planned for VeriStrat testing will be eligible for inclusion into this study.

To determine VeriStrat classification, a small volume of each subject's blood will be processed and collected on a serum card. The serum collection card will immediately be sent to the Biodesix CLIA certified laboratory to determine VeriStrat classification for physician use in subject treatment. If EGFR mutation status has not yet been determined, the GeneStrat test may be performed to support eligibility assessment. An additional card will be spotted and sent to Biodesix for use in research (research card).

Actual physician treatment patterns will be documented and subject disease status and/or survival will be followed for 18 months following entry into the study. Upon progression, or at any time a treatment decision /assessment is being considered, the physician may repeat the VeriStrat test and/or GeneStrat testing (if deemed medically necessary). At this time, the physician will complete the pre-test treatment questionnaire prior to receiving the VeriStrat results. A sample will also be processed for the research card at each treatment decision/assessment time point. Once results are received and treatment has been determined, the actual treatment plan will be completed by the physician. This cycle may be repeated as needed. All eCRFs associated with the study will be completed within 14 days of the visit in accordance with good clinical practices.

Number of Subjects This study will accrue approximately 2,000 subjects.

Subject Population

Inclusion Criteria:

1. Subject must be 18 years of age or older at time of signing informed consent form (ICF).
2. A diagnosis of NSCLC.
3. Subject is willing to provide serum samples for VeriStrat testing.
4. EGFR mutation status wild-type (negative) or a tested unknown.
5. For subjects with untested/unknown EGFR status only: The subject must be willing to provide blood samples for GeneStrat testing.
6. Subject is willing to provide serum samples for research, understanding that no test results will be made available either to the subject or the treating physician.
7. Subject is able to read and understand the ICF and agrees to comply with study procedures and requirements.

Exclusion Criteria:

1. Subject's ability to understand the requirements of the protocol or to provide informed consent is impaired or subject is unwilling to comply with the protocol requirements.

Statistical Methods

Complete details of the statistical analysis will be described in the statistical analysis plan (SAP).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ATQ	Actual Treatment Questionnaire
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
GCP	Good Clinical Practices
HR	Hazard Ratio
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IHC	Immunohistochemistry
Immunotherapy test(s)	Tests in discovery or development, including, for example, BDX008, for classifying immunotherapy-treated subjects by clinical outcome
IRB	Institutional Review Board
MALDI-ToF	Matrix-Assisted Laser Desorption/Ionization–Time Of Flight
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PTQ	Pre-Test Treatment Questionnaire
SAP	Statistical Analysis Plan
TFL	Tables, Figures, and Listings
TKI	Tyrosine Kinase Inhibitor
TTP	Time to Progression
VS	VeriStrat
VS-G	VeriStrat Good
VS-P	VeriStrat Poor

1. INTRODUCTION

1.1. Background

VeriStrat

Taguchi et al, originally established the VeriStrat® (VS) test, as a matrix-assisted laser desorption/ionization–time of flight (MALDI-ToF) mass spectrometry-based test for the analysis of pre-treatment serum that identifies non-small cell lung cancer (NSCLC) patients likely to have good or poor survival outcomes on EGFR-TKIs.¹ The test classifies patients as Good (VS-G) or Poor (VS-P) by comparison of the intensity of eight regions in the mass spectra obtained from patients' serum samples with the intensity of those of an original reference set composed of patients who experienced long-term stable disease (greater than 6 months) and early progressive disease (less than 1 month). In less than 2% of cases, a classification of VS-G or VS-P is not possible and a VeriStrat Indeterminate result is reported. In retrospective^{2,3} and prospective⁴ studies, the VeriStrat test has demonstrated both prognostic significance and utility for predicting clinical benefit from EGFR tyrosine kinase inhibitors (TKI) vs. chemotherapy.

In multiple retrospective analyses of samples from Phase II and Phase III studies, VeriStrat was demonstrated to be a prognostic for survival.^{1-3,5} The largest of these retrospective studies, analysis of pre-treatment samples from a 441 subject subset of NCIC BR.21 trial, demonstrated a significant increase in survival between subjects classified as VS-G and those classified as VS-P.² The VeriStrat test was significantly prognostic for overall survival (OS) in erlotinib-treated subjects independent of clinical covariates. For VS-G subjects, the median survival was 10.5 months on erlotinib versus 6.6 months for placebo (Hazard Ratio [HR] = 0.63, 95% Confidence Interval [CI]: 0.47-0.85, p = 0.002). For VS-P subjects, the median survival was 4.0 months on erlotinib and 3.1 months on placebo (HR = 0.77, 95% CI: 0.55-1.06, p = 0.11).

The prognostic utility of the VeriStrat test was confirmed in TOPICAL, a double-blind randomized placebo-controlled trial of best supportive care plus placebo or erlotinib for chemotherapy-naïve NSCLC subjects (stage IIb/IV) considered unsuitable for chemotherapy.⁵ VeriStrat classification was associated with OS (VS-G vs. VS-P: HR=0.58, 95% CI 0.47-0.73; p<0.001) and PFS (HR=0.72; 95% CI 0.53-0.97; p=0.002). In erlotinib subjects, median OS was 4.9 (VS-G) vs. 3.1 months (VS-P); HR=0.63, 95% CI 0.47-0.85, p=0.002. The corresponding results among placebo subjects were: 5.3 (VS-G) vs. 2.9 months (VS-P), HR=0.53, 95% CI 0.39-0.73, p<0.001. Similar results were found for PFS: median 3.1 (VS-G) vs. 2.2 (VS-P) months (HR=0.72; 95% CI 0.53-0.96, p=0.027) for erlotinib subjects; and 2.8 vs. 2.4 months for placebo subjects (HR=0.72, 95% CI 0.53-0.97, p=0.033).

The prognostic role of the VeriStrat test has also been demonstrated in the front line setting in subjects with NSCLC treated with platinum doublet chemotherapy.^{6,7} A subset of subject samples (n=419) from the Phase 3 NexUS⁸ study of gemcitabine plus cisplatin in combination with sorafenib (Cis/Gem/Sorafenib arm) versus gemcitabine and cisplatin plus placebo (Cis/Gem arm) were available for retrospective VeriStrat testing and results were available for 202 subjects in the Cis/Gem arm. The median PFS for subjects classified as VS-G was 5.7 months (95% CI: 5.5-6.9), while subjects classified as VS-P had a median PFS of 4.6 months (95% CI: 4.1-5.7). PFS was significantly different between groups ($p < 0.001$; HR = 0.51 [95% CI: 0.37-0.71]). Median OS was 15.3 months in the VS-G group and 6.3 months in the VS-P group, and OS was also significantly different between groups ($p < 0.001$; HR = 0.41 [95% CI: 0.30-0.58]).

The Italian cohort (Grossi study) is an ongoing prospective study designed to evaluate the role of the VeriStrat test in first line treatment of NSCLC with standard chemotherapy regimens. An interim analysis of 55 baseline serum samples from subjects with non-squamous histology treated with the combination of carboplatin or cisplatin with pemetrexed demonstrated the prognostic utility of VeriStrat for PFS and OS in this population.⁶ The median PFS for subjects classified as VS-G was 6.1 months (95% CI: 3.9-8.8), while subjects classified as VS-P had a median PFS of 1.3 months (95% CI: 1.0-3.4). PFS was significantly different between groups ($p = 0.0013$; HR = 0.30 [95% CI: 0.15-0.63]). In multivariate analyses, VeriStrat was the only significant predictor of PFS ($p = 0.026$; HR = 0.43 [95% CI: 0.21-0.91]) and OS ($p < 0.001$; HR = 0.20 [95% CI: 0.09-0.47]).

A retrospective analysis of serum or plasma samples from the LCCC0512 study, a randomized phase II trial of first-line treatment with gemcitabine, erlotinib or the combination in elderly (over 70 years old) patients with advanced NSCLC demonstrated that patients with a VS-P status may benefit most from gemcitabine monotherapy.³ In this study, both VeriStrat groups had similar outcomes in the gemcitabine arm. In the erlotinib arm, the VeriStrat Good (n=26) group had significantly better PFS (HR = 0.33; $p = 0.002$) and OS (HR = 0.40; $p = 0.014$) compared with the VeriStrat Poor (n=12) group. In the gemcitabine + erlotinib combination arm, patients with VS Good (n = 17) compared with Poor (n = 15) had a superior PFS (HR = 0.42; $p = 0.027$) and a trend toward superior OS (HR = 0.48; $p = 0.051$). A treatment interaction (gemcitabine versus erlotinib) was observed for PFS and OS. Although within VeriStrat groups, differences in PFS and OS were not significant between treatment arms, the data suggests that that VeriStrat Good patients may benefit most from erlotinib monotherapy and VeriStrat Poor patients may benefit most from gemcitabine therapy. Although the trial size is very small, significance of the interaction between treatment and VeriStrat classification for PFS provides evidence that the VeriStrat test may be predictive between erlotinib and gemcitabine monotherapies.

The VeriStrat test is also the first prospectively validated test that provides additional information to assist in treatment decisions in subjects with advanced NSCLC who are EGFR wild-type, or whose

EGFR mutational status cannot be obtained, following progression on platinum-based chemotherapy. VeriStrat was predictive for OS in the prospective, randomized, VeriStrat-stratified, Phase III study of 2nd line erlotinib versus single-agent chemotherapy in subjects with inoperable NSCLC (PROSE).⁴ In this study, subjects with a classification of VS-P had worse OS on erlotinib than on chemotherapy (HR = 1.72, [95% CI 1.08-2.74], p=0.022) while there was no significant difference in OS between treatments for subjects classified as VS-G (HR = 1.06, [95% CI 0.77-1.46], p=0.714). The interaction between treatment and VeriStrat classification was significant when adjusted (p=0.017) or unadjusted (p=0.031) for stratification factors. As of October of 2014, the National Comprehensive Cancer Network (NCCN) Guidelines recommend proteomic testing for subjects with advanced NSCLC who test negative for EGFR mutations or whose EGFR mutation status is unknown. A patient with a ‘poor’ classification should not be offered erlotinib in the 2nd-line setting.

Validation of Tests for Selection of Subjects Treated with Immunotherapies

The use of immune checkpoint inhibitors, including regulatory approvals of immunotherapy for melanoma (ipilimumab, nivolumab, pembrolizumab)⁹⁻¹¹ and non-small cell lung cancer (NSCLC [nivolumab, pembrolizumab])^{12,13}, is transforming cancer treatment. Although immunotherapies represent a significant advancement, response to these cancer treatments remains variable. The response rate to the PD-1 immune checkpoint inhibitors in advanced melanoma is approximately 30 to 40%^{10,11}, and approximately 19% for 2nd-line therapy in NSCLC¹⁴. Thus, the ability to identify the subset of patients who respond to anti-PD-1 therapy remains a critical unmet need.

Efforts to develop biomarkers that identify the subset of patients who respond to therapy have focused on tumor cell surface expression of PD-L1 as assessed by immunohistochemistry (IHC). Challenges with IHC as a predictive biomarker for anti-PD-1/PD-L1 treatment include the availability of tissue, heterogeneity of PD-L1 expression, and applicability across different staining platforms and cancer types. Most importantly, response to immunotherapy is the result of the complex interplay between the tumor, the tumor microenvironment, and host immune system¹⁵ and will be better captured by a multivariate test. To that end, Biodesix is developing blood-based, multivariate proteomic tests based on a matrix-assisted laser desorption/ ionization time-of-flight (MALDI-ToF) mass spectrometry measurement.

For example, preliminary data demonstrates that the newly-developed BDX008 test, can stratify subjects with advanced melanoma according to survival outcomes following immunotherapy treatment. BDX008 utilizes pre-treatment serum samples, deep MALDI¹⁶, and an algorithm to stratify subjects based on the likelihood of having better or worse outcomes. The test is binary, producing one of two results: BDX008+ or BDX008-^{17,18}. Initial development of the test was performed using 119 pre-treatment serum samples collected in a study evaluating nivolumab with or without a peptide vaccine in subjects with unresectable stage III or stage IV melanoma¹⁹. In the cohort as a whole, median time

to progression (TTP) was 160 days and median overall survival (OS) was 94 weeks. The test assigned 61% of samples a BDX008+ classification and 39% of samples a BDX008- classification. Significantly longer overall survival was observed in the BDX008+ group (median OS not reached) as compared to the BDX008- group (median OS 61 weeks), with a hazard ratio of 0.38 (95% CI = 0.19-0.55, $p < 0.001$). Similarly, TTP in the BDX008+ group (median 230 days) was longer than that in the BDX008- group (median 84 days, HR [95%CI] = 0.50 [0.29-0.71], $p = 0.001$).

Thirty pre-treatment samples from subjects with advanced melanoma treated with anti-PD-1 antibodies were used as an independent validation cohort¹⁸. Thirty-Three percent were designated as BDX008- with a hazard ratio for OS between classification groups of 0.27 (95% CI = 0.05-0.52, $p = 0.002$) and a difference in median survival between groups in excess of three years. These initial studies demonstrate that the classifier (BDX008 status) reliably identifies melanoma subjects who have longer OS and TTP following treatment with PD-1 inhibitors, however, data for NSCLC subjects is lacking.

1.2. Study Rationale

The primary purpose of this observational study is to assess the physician's clinical practice patterns while using the VeriStrat test in subjects with NSCLC whose tumors are EGFR wild-type (negative) or have unknown EGFR mutational status. This study will also attempt to further validate that the VeriStrat test stratifies subjects by clinical outcomes in the uncontrolled clinical setting while exploring if certain therapeutic approaches may yield opportunities for further study.

Predictive and prognostic tests that aid in therapeutic decision making are critical for optimizing patient outcomes while minimizing toxicity and associated treatment costs. This study will provide data for the development and validation of Biodesix immunotherapy tests, including BDX008. Immunotherapy mechanisms are dependent upon the interactions between the tumor, tumor microenvironment, and the host immune system¹⁵. As such, a successful predictive test will reflect the complex interplay between tumor and host. The multivariate tests from Biodesix have the advantage of being able to assess this complex biology.

The information gained from this research will not only guide the adoption of the VeriStrat test and inform medical decision making, including treatment choice, but will allow the validation of additional mass-spectrometry-based proteomic tests.

2. STUDY OBJECTIVES

2.1. Primary Objective

- 2.1.1. To describe physician treatment patterns pre- and post- VeriStrat testing at time of treatment decision or assessment.

2.2. Secondary Objectives which may be tested

- 2.2.1. To determine whether immunotherapy test(s) stratify immunotherapy-treated subjects by overall survival.
- 2.2.2. To determine whether immunotherapy test(s) stratify immunotherapy-treated subjects by progression-free survival.
- 2.2.3. To compare outcomes between those classified as VeriStrat-Poor and VeriStrat-Good.
- 2.2.4. To compare outcomes in subjects classified as VeriStrat-Poor and VeriStrat-Good and treated with platinum-based therapy.
- 2.2.5. To compare outcomes in subjects classified as VeriStrat-Poor and VeriStrat-Good and treated with immunotherapy.
- 2.2.6. To compare outcomes in subjects classified as VeriStrat-Poor and VeriStrat-Good and treated with single agent chemotherapy.
- 2.2.7. To evaluate the longitudinal changes in VeriStrat classification over the course of the study.

2.3. Exploratory Objectives which may be tested:

- 2.3.1. To determine whether immunotherapy test(s) stratify subjects treated with chemotherapy or targeted therapies by outcome.
- 2.3.2. To observe the correlation between VeriStrat classification and immunotherapy test(s) classification at baseline and longitudinally.
- 2.3.3. To describe the longitudinal changes in immunotherapy test classification over the course of the study.
- 2.3.4. To determine whether immunotherapy test(s) stratify immunotherapy-treated subjects by other clinically meaningful factors or endpoints.
- 2.3.5. To observe changes in GeneStrat status across lines of therapy.

3. STUDY PLAN

The study will include approximately 25-35 sites in the US. The study sites will obtain approval from an Institutional Review Board (IRB) prior to initiating the study.

It is estimated that this study will accrue up to approximately 2,000 subjects. In order to appropriately assess the study objectives related to VeriStrat, GeneStrat and new biomarkers, subjects will be tracked according to their treatment. The actual treatment plan for each subject will be at the treating physician's discretion.

Subjects who have been diagnosed with NSCLC, at any line of treatment, are EGFR wild-type (negative) or tested unknown, and are planned for VeriStrat testing will be eligible for inclusion into this study. Treating physicians will need to identify the EGFR mutation status of the subject before the VeriStrat classification is completed as part of assessing eligibility for study entry. If EGFR mutation status is unknown when the patient is being considered for study enrollment, GeneStrat testing can be requested at the same time as VeriStrat testing. Alternatively, treating physicians may determine the EGFR mutation status before ordering the VeriStrat test.

If EGFR status is known to be negative at the time of study entry the subject may be directly enrolled into the study using Option 1, Direct Enrollment, described below in **Figure 1**. If GeneStrat was previously ordered (including but not limited to EML-4ALK Fusions, KRAS, BRAF, ROS1, RET and EGFR) as part of routine care, this data may be reviewed by Biodesix for use in further test validation and/or exploratory research.

If EGFR status has not been assessed at the time of study entry, GeneStrat may be ordered to assess the EGFR status, the subject may enter the study as Option 2, EGFR Screening, as described in **Figure 1**. If the treating physician's practice incorporates the use of a combination genomic-proteomic test (i.e., GeneStrat/VeriStrat reflex testing) to assess the EGFR mutation status of a subject, then the treating physician should obtain and process the blood samples for GeneStrat, VeriStrat and research according to the instructions provided by Biodesix. If the GeneStrat results identify an EGFR status of wild-type (negative) or status unknown, and all other inclusion/exclusion criteria have been confirmed, the subject will be enrolled into the study and VeriStrat and the research card will be analyzed. Those previously-consented subjects who are identified as having an EGFR mutation status of positive (EGFR+) will be considered a screen failure, and will not be enrolled into the study. The VeriStrat test and the research card will be discarded according to standard laboratory procedures.

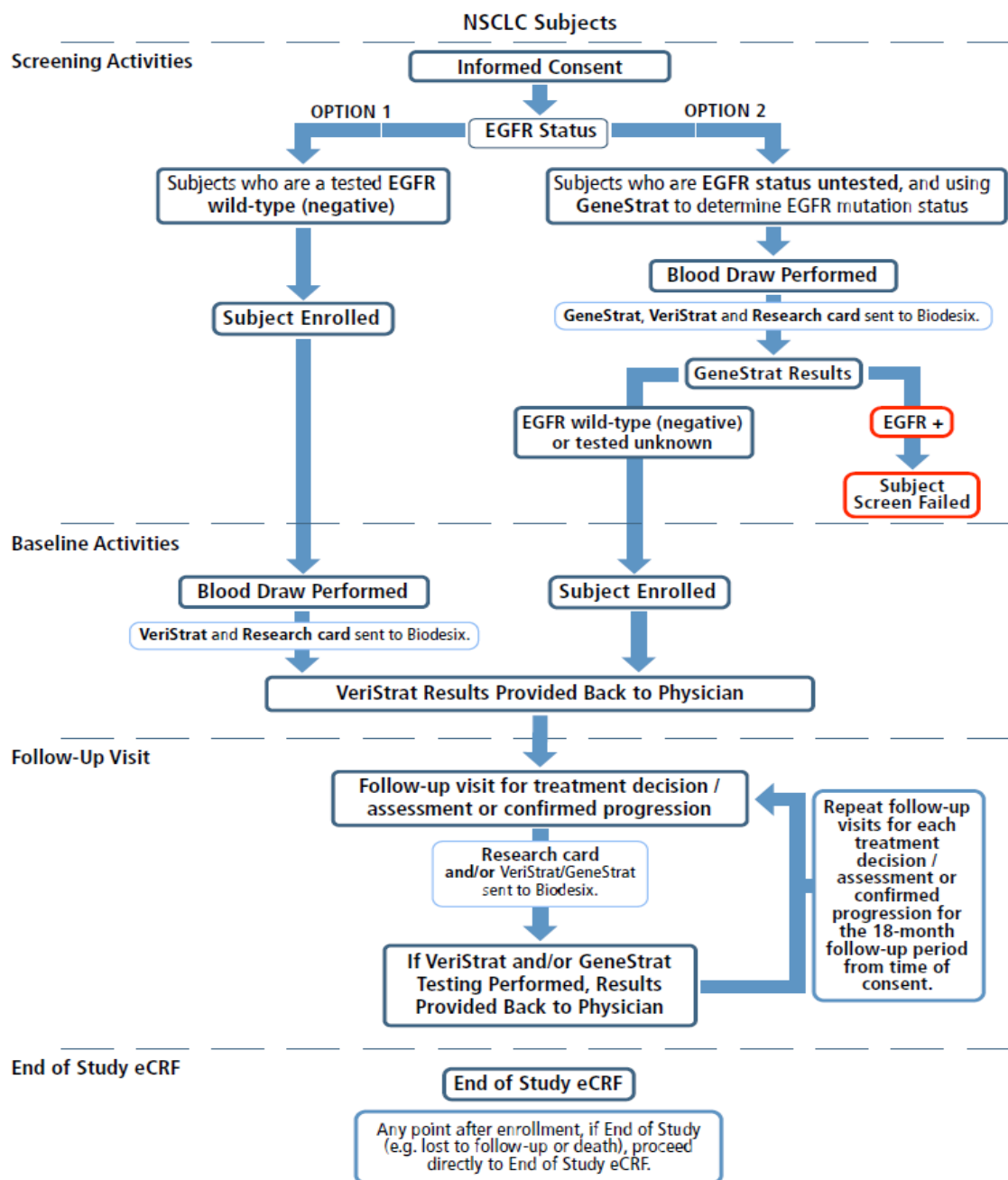
To determine VeriStrat classification, a small volume of each subject's blood sample will be collected on a serum collection card using a collection kit provided by Biodesix. A second serum collection card

will be spotted for research use. Sample collection and processing instructions will be provided by Biodesix. The serum collection cards will immediately be sent to Biodesix's CLIA-certified laboratory. The VeriStrat classification will be immediately processed for physician use in treatment decisions/assessments. The research card will be processed according to research procedures and results will not be provided back to the physician or subject as it is for use in research.

At the time of EGFR screening or direct enrollment and before receiving the VeriStrat results, the physician or designee will complete a pre-test treatment questionnaire (PTQ). Only subjects who are consented and have a PTQ completed before the treating physician receives the VeriStrat results will be included in the primary objective analysis. In the event a newly- diagnosed subject has arrived at the treating oncologist's office with VeriStrat results in hand, (as potentially ordered by a pulmonologist or thoracic surgeon or other qualified health professional) the subject will be allowed into the study, provided a signed informed consent form (ICF) is obtained and all other eligibility criteria are met. The PTQ data related to the subject's baseline visit will not be used for primary objective analysis as the investigator may be biased in providing a response to the PTQ. The subject's results and clinical data will be used for the secondary and exploratory objectives as they are available and meet analysis requirements.

Actual physician treatment patterns will be documented and the subject will be followed for up to 18 months following entry into the study (the date the ICF was obtained). Upon each treatment decision /assessment; the physician may request the VeriStrat test and/or the GeneStrat test for use in patient treatment (if deemed medically necessary), spot an additional serum card for research, and complete the PTQ prior to receiving the VeriStrat results. Once VeriStrat results are received and treatment has been determined, the eCRF should be updated with the actual treatment administered. This cycle may be repeated until the 18-month follow-up period has ended or subject expiry. If the physician does not choose to use the VeriStrat test for patient care, the data from the research card may be used to assess the secondary and exploratory objectives. See **Figure 1** for the study diagram. If the subject entered the study in a previous line of therapy and the treating physician chooses to order the GeneStrat test at progression or other time of treatment assessment and an EGFR mutation is identified, the subject will NOT be discontinued from the study, but will be continue as per above protocol instruction

Figure 1: Study Diagram



Non-standard clinic visits are not required for the study. See **Table 1** in the Appendix for the schedule of assessments and procedures. It will be the responsibility of the investigative site to record the subject's status (as applicable) at regularly scheduled clinic visits until death or 18 months after the date the subject signed the ICF, whichever comes first. Subject status information will be recorded on the eCRF including date of status update, treatment decision details and/or death.

For the purposes of this study, it is permissible to record death status based on a documented record of any telephone conversations that occur between the site and the subject or the subject's family members or designee per their medical release on file with the treating institution.

4. POPULATION

4.1. Inclusion Criteria:

- 4.1.1. Subject must be 18 years of age or older at time of signing informed consent.
- 4.1.2. A diagnosis of NSCLC.
- 4.1.3. Subject is willing to provide serum samples for VeriStrat testing.
- 4.1.4. EGFR mutation status wild-type (negative) or unknown.
- 4.1.5. For subjects with untested/unknown EGFR status only: The subject must be willing to provide blood samples for GeneStrat testing.
- 4.1.6. Subject is willing to provide serum samples for research, understanding that no test results will be made available either to the subject or the treating physician.
- 4.1.7. Subject is able to read and understand the ICF, and agrees to comply with study procedures and requirements.

4.2. Exclusion Criteria

- 4.2.1. Subject's ability to understand the requirements of the protocol or to provide informed consent is impaired or subject is unwilling to comply with the protocol requirements.

5. STUDY VISITS AND PROCEDURES

5.1. Direct Enrollment (Option 1) EGFR Status negative or a tested unknown.

5.1.1. Baseline Activities Visit

Complete the following procedures prior to starting treatment.

- 5.1.1.1. Obtain signed informed consent prior to performing any study procedures.
- 5.1.1.2. Confirm that the subject meets all eligibility requirements.

- 5.1.1.3. Collect venous blood into blood tubes provided by Biodesix. The serum from this blood draw will be used for both the VeriStrat test and the research card. Process using the materials and instructions provided by Biodesix.
- 5.1.1.4. After collecting venous blood and processing the sample, ship the VeriStrat test and research serum cards directly to Biodesix according to the instructions provided by Biodesix.
- 5.1.1.5. The physician or designee must complete the Pre-Test Treatment Questionnaire(PTQ) prior to reviewing the VeriStrat results.
- 5.1.2. After Receipt of the VeriStrat Results (Baseline Continued)
 - 5.1.2.1. Complete the Actual Treatment Questionnaire eCRF for treatment chosen by the treating physician.
- 5.2. EGFR Screening (Option 2) EGFR status has never been tested and is unknown.
 - 5.2.1. Screening Activities Visit
 - 5.2.1.1. Obtain signed informed consent prior to performing any study procedures.
 - 5.2.1.2. Confirm that the subject meets all eligibility requirements (except EGFR mutation status).
 - 5.2.1.3. Collect venous blood into the blood collection tubes provided for GeneStrat and VeriStrat and the research card. Process using the materials and instructions provided by Biodesix.
 - 5.2.1.4. After collecting venous blood and processing the sample, ship VeriStrat, research serum card, and GeneStrat tubes directly to Biodesix according to the instructions provided by Biodesix.
 - 5.2.1.5. The physician or designee must complete Pre-Test Treatment Questionnaire (PTQ) eCRF prior to receipt of any results.
 - 5.2.2. Enrollment Assessment after Receipt of Results (Screen Failure or Baseline Activities)
 - 5.2.2.1. Screen Failure (EGFR Mutation Positive)
 - 5.2.2.1.1. If the subject has been identified as EGFR Mutation Positive, complete the eCRFs for the Screening Activities visit. The subject is considered ineligible for the study, and no further activities are required for this subject.
 - 5.2.2.2. Eligibility Confirmed (EGFR wild-type (negative) or Status Unknown – Baseline Activities Visit)
 - 5.2.2.2.1. If the subject has been identified as EGFR wild -type or status unknown, confirm remaining eligibility requirements and enroll subject into the study.

5.2.2.2.2. Complete the eCRFs for the Baseline Activities visit which includes demographic information and NSCLC-related medical history.

5.2.2.2.3. Complete the Actual Treatment Questionnaire eCRF as decided by the treating physician.

5.3. Subject Follow-up Visits/Death

Complete the following when the physician is considering a treatment decision or at subject death, up to a maximum of 18 months after signing ICF:

5.3.1. Complete the Follow-Up eCRFs.

5.3.2. Collect venous blood into the blood tubes provided by Biodesix. If the physician has decided to run the VeriStrat test to assist in making a treatment decision, then process the sample for both VeriStrat and the research card using the materials and instructions provided by Biodesix. If not, process the sample ONLY for the research card.

5.3.3. If the physician has decided to run the GeneStrat test at a treatment decision making time point, collect venous blood into the blood tubes for GeneStrat. Process using the materials provided by Biodesix.

5.3.4. After collecting venous blood and processing the samples for the appropriate tests, ship directly to Biodesix according to the instructions provided.

5.3.5. If the physician ordered the VeriStrat test as part of routine care, the physician or designee must complete the PTQ prior to reviewing the VeriStrat test results.

5.3.5.1. Upon receipt of the VeriStrat test results, the physician or designee must complete Actual Treatment Questionnaire eCRF.

5.3.6. If the physician did not order the VeriStrat test, complete the Actual Treatment Questionnaire eCRF.

5.3.7. Complete End of Study eCRF including date of death, as applicable.

See **Table 1** in the Appendix for the schedule of assessments and procedures.

6. STATISTICAL ANALYSES

The statistical analysis will be detailed in the SAP. The SAP will provide a full description of the statistical methods for the analyses as outlined below; additional analyses may be added. The SAP will contain table, figure, and listing (TFL) shells for programming the analyses.

6.1. Demographics and Baseline Characteristics

Categorical variables will be summarized using the number and percentage of subjects falling into each category and continuous variables will be summarized using mean, standard deviation, median, minimum, maximum, and the number of subjects with available data.

6.2. Primary & Secondary Analyses

Pre- and post-test treatment plans will be correlated by subject and tabulated. Changes between pre-test and post-test treatment plans will be compared between subjects classified as VeriStrat Good and VeriStrat Poor using Fisher's exact test or other suitable statistical tests.

Survival analysis will be completed to compare time to outcome events such as OS and PFS. To compare the survival curves between two groups, a statistical test such as the log-rank test will be employed.

6.3. Missing Data

Details on the handling of missing data will be described in the SAP. Variables will be summarized for all eligible subjects with available data. For all key variables, the proportion of missing data will be described to understand the extent to which there may be under-reporting or bias.

Missing data in the eCRF will be detected via remote monitoring, and follow-up will be conducted as outlined in the Site Management Plan. In general, missing data will not be imputed and the data will be analyzed as they are recorded in the eCRFs. The impact of missing data on the analysis will be discussed, and the pattern of missing data will be explored.

6.4. Data Reporting

Results of the effectiveness analyses will be summarized for all eligible subjects with available medical record data, and submitted in the form of a final study report at the end of the study (following database lock), regardless if the study is completed or prematurely terminated.

The results obtained within the study are the exclusive property of the Sponsor. The Sponsor recognizes the ethical obligation to disseminate findings of potential scientific or public health importance, including publication of the results in peer-reviewed literature. Specific plans for disseminating and communicating the information will be provided when study results are available.

7. DATA HANDLING AND QUALITY ASSURANCE

7.1. Case Report Forms

Required information will be entered into the appropriate eCRF in the Electronic Data Capture (EDC) system. All eCRFs are to be completed accurately and promptly, and should be updated as needed so they reflect the latest information in the subject's medical record. All records are to be kept in conformance with applicable guidelines and standard operating procedures.

7.2. Assessment and Reporting of Adverse Events

The investigator will determine the seriousness, intensity, and causality of an adverse event associated with the use of VeriStrat, GeneStrat and/or the research card. All related adverse events should be reported to Biodesix through normal commercial reporting processes by calling Biodesix Customer Support at 1-866-432-5930. The investigator may also consult Biodesix Medical Affairs for support in adverse event handling.

Reportable events, though unlikely, could conceivably still arise in this research (e.g., protocol deviations, unexpected breach of confidentiality, a serious adverse event from a blood draw, miscommunication of test results, etc.). Any event involving the rights, safety, and welfare of participants or study integrity that is deemed reportable should be submitted to IRB for review.

7.3. Monitoring of the Study

Biodesix will be responsible for monitoring the study to ensure the overall completion and accuracy of the data. Biodesix and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities, and upon request, inspecting the various records of the study. Biodesix is responsible for reviewing the eCRFs data during the study to verify adherence to the protocol; completeness, accuracy, and consistency of data; and adherence to Good Clinical Practices (GCP). Upon request, the sponsor's monitor should receive access to subject medical records and other study-related records needed to verify entries on the eCRFs. By signing the investigator statement of protocol approval, the investigator agrees to cooperate with the staff of Biodesix. The frequency of monitoring visits will be based on site subject enrollment numbers as well as overall study performance.

7.4. Inspection of Records

All investigative site staff involved in the study will permit study-related audits, IRB review, and regulatory inspections by providing direct access to all study records. Biodesix or its designee may monitor or audit all study records. In the event of an audit or regulatory inspection, the principal investigator (PI) agrees to allow Biodesix and its designees or regulatory agencies access to all study records. The PI should promptly notify Biodesix of any inspections scheduled by any regulatory authorities and promptly forward copies of any documentation received for such purposes to Biodesix.

7.5. Study Record Retention

Essential documentation should be retained for 10 years, unless otherwise designated by Biodesix. When the study is completed, the investigator must retain the essential documents for as long as needed to comply with FDA guidelines and sponsor requirements. The investigator shall notify the sponsor prior to moving or destroying any of the study documents.

8. ADMINISTRATIVE CONSIDERATIONS

The following administrative items are meant to guide the PI in the conduct of the study but may be subject to change based on industry and government standard operating procedures or working practice documents or guidelines.

8.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for collecting data, auditing by Biodesix, its designee, the IRB, or applicable regulatory authorities and within the scope of federal guidelines including but not limited to the Health Insurance Portability and Accountability Act (HIPAA).

The investigative sites including but not limited to, their employees, owners, agents and contractors involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purposes of this study. Prior written agreement from Biodesix or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2. Institutional Review Board Approval

Federal regulations, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines require that approval be obtained from an IRB before participation of human subjects in research studies commences. Before the study begins, the protocol, ICF, any written study information to be provided to the subject or the subject's legal guardian, and any advertisements used for study recruitment must be approved by the IRB. In addition, such documentation, as well as that of the IRB compliance with institutional and regulatory regulations, will be maintained by the site and will be available for review by Biodesix, its designee or applicable regulatory authorities.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted.

Each investigative site is responsible for assuring continued approval of the study at intervals not exceeding one year or otherwise specified by the IRB.

8.3. Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject must be reviewed and approved by Biodesix. Amendments to the protocol must be submitted in writing to the appropriate IRB for approval before subject enrollment into an amended protocol.

8.4. Informed Consent

A signed ICF shall be obtained from each subject before entering the study or performing any study-specific or non-routine procedure that involves risk to the subject. If any modifications are proposed or made to the template language by the site, Biodesix shall review and provide approval of the modified ICF prior to IRB submission. Once reviewed, the ICF will be submitted by the PI to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, active participating subjects may be required to sign the revised ICF depending on the nature and substance of the changes made.

Before study enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study by the Investigator or a member of his or her research team, and will be allowed to read the IRB-approved ICF. Once the PI is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The PI shall provide a copy of the original, signed ICF to the subject and/or legal guardian. An original shall be maintained in the subject's study records at the site.

8.5. Study Reporting Requirements

By participating in this study, the PI agrees to submit annual reports to his or her IRB as appropriate.

8.6. Study Conduct

The PI agrees that the study will be conducted according to the principles of GCP and ICH, as specified, and the principles of the Declaration of Helsinki. The PI will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

8.7. Publications

After completion of the study, the study data may be considered for reporting at one or more scientific meetings and/or for publication in scientific journals. Biodesix will be responsible for these activities and will determine how any publication is written and edited, the number and order of authors, the meetings and/or journals to which it will be submitted, and other related issues. Biodesix has final approval over all such issues when any of our products are included.

Each investigative site will have access to their study data and Biodesix. All study data is the property of Biodesix and cannot be published without prior authorization from Biodesix, but data and approval for publication thereof will not be unduly withheld.

9.0 Revision History

Date	Version	Modified by	Description of Changes/ rationale	Approval
3/30/2016	V1.0		Original	Kat Kwiatowski
3/20/2017	V2.0	Kelsy Snyder	<ol style="list-style-type: none">1. Section 3 Study Plan, paragraph 4: Replace “(e.g. EML-4ALK Fusions, KRAS, and EGFR)” with “(including but not limited to EML-4ALK Fusions, KRAS, BRAF, ROS1, RET and EGFR)”2. Section 5.1.1.4. replace “Collect venous blood into the 4.0 mL SST Vacuette” with “Collect venous blood into a SST Vacuette.”3. Section 5.2.1.3. replace “Collect venous blood into two 10.0 mL Streck tubes (1 DNA and 1 RNA) for GeneStrat and one 4.0 mL SST Vacuette for VeriStrat and the research card” with “Collect venous blood into blood collection and serum separator tubes provided for GeneStrat and VeriStrat and the research card. “4. Section 5.3.2. replace “Collect venous blood into the 4.0 mL SST Vacuette” with “Collect venous blood into a SST Vacuette.”5. Section 5.3.3. replace “If the treating physician has chosen to run GeneStrat at progression, collect venous blood into	Linda Traylor

			two 10.0 mL Streck tubes (1 DNA and 1 RNA) for GeneStrat” with “If the treating physician has chosen to run GeneStrat at progression, collect venous blood into Streck tubes for GeneStrat.”	
9/7/2017	V3.0	Niki Givens	<ol style="list-style-type: none"> 1. Protocol Title and throughout the text- two additional words added for clarity, “the VeriStrat Test” instead of only VeriStrat. The VeriStrat test is more grammatically correct and adds clarity. 2. Investigator statement of Protocol Approval- added “version 3 and the new protocol approval date, for clarity of protocol version. 3. Protocol Synopsis- Primary Objective, changed the wording from “each line of therapy” to read “time of treatment decision or assessment” because it better describes the treatment change timing; many treatment decisions were being missed because the “each line of therapy” language was confusing to research coordinators. 4. Protocol Synopsis, Secondary Objective, number 6- removed the word gemcitabine and replaced with single agent chemotherapy. Gemcitabine is too specific, single agent chemotherapy is more appropriate and covers more therapy types. 5. Protocol Synopsis, Secondary Objectives number 7 – replaced the word compare with evaluate; evaluate is more appropriate for the statistical analysis. 6. Protocol Synopsis, Study Design- added the word negative behind “wild-type” for protocol clarity. Removed the wording “for the validation of Biodesix immunotherapy tests, including BDX008 and changed to “to support Biodesix new classifier development” for clarity purposes. Various other small wording changes made to aid in study understanding. 7. Protocol Synopsis, Number of Subjects- Changed the number from approximately 1000 subjects to 2000 subjects. Interim analysis of primary objective data indicates that the collection of additional subjects will benefit the primary, secondary and exploratory objectives. 	Linda Traylor

			<ol style="list-style-type: none">8. Protocol Synopsis, Inclusion criteria, removed “If subject has had prior treatment for local disease, disease progression was documented and treatment was completed prior to VeriStrat testing”. Removed because it doesn’t impact the primary objective, there is no evidence that VeriStrat is impacted by treatment in local disease. Added some language to inclusion criteria numbers 4 and 5 to add clarity.9. Protocol Synopsis, Exclusion criteria, removed “History of prior malignancy within 2 years of signing ICF (except for adequately treated non-melanoma skin cancer, carcinoma in situ of the breast or cervix, superficial bladder cancer, or early stage prostate cancer, without evidence of recurrence) – as long as the patient is being treated as a lung cancer patient, history of malignancy is not relevant to the evaluation of the primary or secondary objectives, but will be captured in medical history.10. Introduction Sections 1.1 and 1.2, some wording added for clarity and better grammar.11. Study Objective Section 2.1.1 removed “each line of therapy” and replaced with “time of treatment decision or assessment” because it better describes the treatment change timing, many treatment decisions were being missed because of the “each line of therapy” language. This change has been made through-out the protocol.12. Study Objective Section 2.2.6- removed “gemcitabine” replaced with “single agent chemotherapy” Gemcitabine was too specific, single agent chemotherapy is more appropriate and covers more therapy types.13. Study Objective Section 2.2.7 – replaced the word compare with evaluate. Evaluate is more appropriate for the statistical analysis.14. Section 3, Study Plan - Increased the number of expected study accrual from 1000 to 2000 subjects. Interim analysis of primary objective data indicates that the collection of additional subjects will benefit the primary, secondary and exploratory objectives.	
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			<ul style="list-style-type: none">15. Study Plan, Section 3 - added wording to add clarity.16. Study Plan, Sections 3 Figure 1 – replaced the figure to make it more readable and clear.17. Inclusion Criteria, Section 4 - removed 4.1.7. “If subject has had prior treatment for local disease, disease progression was documented and treatment was completed prior to VeriStrat testing”. Removed because it doesn’t impact the primary objective, there is no evidence that VeriStrat is impacted by treatment in local disease.18. Section 4, Population, Exclusion Criteria removed 4.2.1, “History of prior malignancy within 2 years of signing ICF (except for adequately treated non-melanoma skin cancer, carcinoma in situ of the breast or cervix, superficial bladder cancer, or early stage prostate cancer, without evidence of recurrence)- as long as the patient is being treated as a lung cancer patient, history of malignancy is not relevant to the evaluation of the primary or secondary objectives, but will be captured in medical history.19. Section 5.1.1.3 replaced “serum separator tubes” with “blood tubes provided by Biodesix”, the specific tube type is not necessary.20. Section 5.1.1.5 added the Pre-Test Treatment Questionnaire, to make the expectation clearer.21. Sections 5.1.2.1 and 5.2.2.2 added some wording to increase the clarity of the protocol.22. Section 5 Study Visits and Procedures, section 5.3, changed the word Progression to Follow-up. Follow-up better describes the type of visit that pertains to the protocol.23. Section 5 Study Visits and Procedures, sections 5.3.2, 5.3.3, and 5.3.51, the word progression was changed to treatment decision/ assessment. The new wording better describes the type of visit that pertains to the protocol.24. Section 9, Revision History added for clarity of changes made to the protocol.	
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			25. Appendix Table 1. Schedule of Assessments and Procedures, the word progression was changed to Follow-up, this better describes the type of visit that pertains to the protocol.	
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9. APPENDIX: TABLE 1 schedule of assessments and procedures

	DIRECT ENROLLMENT (Option 1) Baseline Activities	EGFR SCREENING (Option 2) Screening Activities ¹	EGFR SCREENING (Option 2) AFTER EGFR Mutation Status has been Determined¹ Enrollment Assessment Baseline Activities	Subject Follow-Up Visits ⁴	Death Recording / End of Study Visit
Informed Consent	X	X			
Eligibility Assessment/Confirmation	X	X	X		
EGFR Status Assessment	X	X			
Subject Blood Draw	X	X		X	
Process Blood for GeneStrat		X		X (Optional)	
Process Blood for VeriStrat	X	X		X (Optional)	
Process Serum Card for Research	X	X		X	
Demographics	X	X			
NSCLC Medical History	X		X		
Pre-Test Treatment Questionnaire (PTQ)	X ²	X		X ²	
Actual Treatment Questionnaire	X ³		X	X ³	
Follow-up Visit- Treatment decision/ assessment /progression				X	
End of Study / Death Details (if applicable)					X

¹GeneStrat testing performed after consent if subject does not have mutation status and the treating physician was planning to use GeneStrat/VeriStrat reflex testing as a part of the care plan. Treating physicians will not enter NSCLC demographics and medical history in the eCRF until results are received and the subject is confirmed eligible.

²PTQ should be completed prior to receiving VeriStrat results, unless the subject arrived in the treating oncologist's office with results in hand. At Follow-up visits, VeriStrat is optional. If physician did not order VeriStrat, PTQ will not be completed.

³Actual Treatment plan should be completed after receipt of results (if VeriStrat ordered), otherwise at the Follow-up visit.

⁴Follow-up visits should be repeated as needed and up to 18 months after signing the ICF.